PATENT APPLICATION
Docket No. SPC89-05'
Expedited Procedure Under 37 C.F.R. 1.116
Examining Group 1205

#29
JRP
7/30/93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on July 23, 1993
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

B.J. Kenney July 23, 1993
Signature Date

DECLARATION

The Honorable Commissioner
of Patents and Trademarks
Box AF
Washington, D.C. 20231

Dear Sir:

I, Gunnar Aberg, declare:

THAT I am a citizen of Sweden and a resident of the Town of Westborough, Worcester County, Massachusetts;

THAT I am Vice-President of Research and Development, Pharmaceutical Division, Sepracor, Inc., Marlborough, Massachusetts. From 1968 to 1973 I was Director of Pharmacology at Bofors-Nobel Pharma, from 1974 to 1978 I was Group Leader in General Pharmacology at AB Haessle, from 1978 to 1980, I was Director of Pharmacology at Astra Pharmaceuticals, from 1980 to 1982 I was Director of Cardiovascular Pharmacology at Ciba-Geigy;

and from 1982 to 1988 I was Director of Pharmacology, and from 1988 to 1992 Executive Director of Pharmacology, at Bristol-Myers Squibb;

THAT I am a graduate of the University of Linkoping, Sweden from which I hold a Ph.D. in Pharmacology and of the University of Goteborg, Sweden from which I hold a Ph.D. in Zoophysiology, and that I hold the title of Docent (Associate Professor) in Applied Pharmacology at the University of Linkoping, Sweden;

THAT I have twenty-five years' industrial experience in the area of research pharmacology;

THAT I am an author of 86 articles on pharmacology, including ten articles on adrenergic β-blockers and β-agonists and that I am an inventor on seven U.S. patents and six pending U.S. applications and that I have made numerous presentations before professional societies and in universities on the subject of adrenergic drugs;

THAT I have reviewed the Office Action dated June 7, 1993 in the above case. I have also reviewed the application in the above case and the publications of Morley et al. [Brit. J. Pharmacol. 104, Suppl. 295P (1991)] and Chapman et al. [Trends in Pharmacological Science 12 231-232 (1992)], and as a result of my review and general knowledge of the subject area, I make the following analysis:

In the instant application, Barberich and Young disclose an unexpected diminution in side effects when the pure R-isomer of albuterol is administered. The literature cited in the office action, which was published prior to applicants' filing date, provides no evidence for an advantage of either enantiomer of albuterol on the basis of β_1 vs β_2 specificity.

The above-identified recent publications of Morley et al. and Chapman et al. provide newly available support for applicants' disclosure. These references disclose that the S(+) isomer of albuterol in guinea pigs causes a hypersensitivity to allergen. The authors concluded from their experiments that the

desired bronchodilator effect was prone to tachyphylaxis while the undesirable hypersensitivity to spasmogens was less prone to tachyphylaxis. Indeed, in the Chapman et al. paper the authors recommend that it may be prudent to remove enantiomers that were previously thought to be biologically inert. Their results support a previously undisclosed advantage to the use of pure R-enantiomer in that the side effect of paradoxical hypersensitivity is likely to be ameliorated.

Since the studies by Morley and Chapman were all performed *in vivo*, studies have now been performed under my direct supervision to investigate the effects of the albuterol isomers on bronchial smooth muscle preparations *in vitro*. These experiments were performed to determine whether the mechanism by which S(+)albuterol increased airway resistance was a direct effect on bronchial smooth muscle or was due to some undefined mechanism that may be species-specific to guinea pigs.

In these experiments, isolated tracheal muscle preparations were repeatedly subjected to graded doses of spasmogens, such as carbacholine. (It has been shown in previous studies that the effects of betareceptor agonists on isolated bronchial smooth muscle preparations are similar in human and guinea pig preparations.) After the tissues had been caused to contract, with increasing concentrations of carbacholine (10^{-8}M to 10^{-6}M), they were washed and some tissues were incubated for 90 min. with RS-, R(-), or S(+) albuterol at a concentration of 10^{-6}M, while other tissues were control tissues, incubated with the Ringer solution only. After the incubation period, the tissues were again carefully washed and subjected to renewed contractions with the spasmogen.

Results are presented in Figs. 1 through 4. It was found that the contractile response to the spasmogen was significantly ($P < 0.01$) increased in bronchial tissue strips that had been incubated with S(+)albuterol. No such effect was seen in tissues that had been incubated with R(-)albuterol, while the sensitizing

effect of the racemate was masked by the presence of the bronchodilating effect of the R(-) isomer. One may therefore conclude that the increased sensitivity to spasmogens by S(+)albuterol is due to direct effects on bronchial smooth muscles, rather than to undefined and possibly species-specific mechanisms.

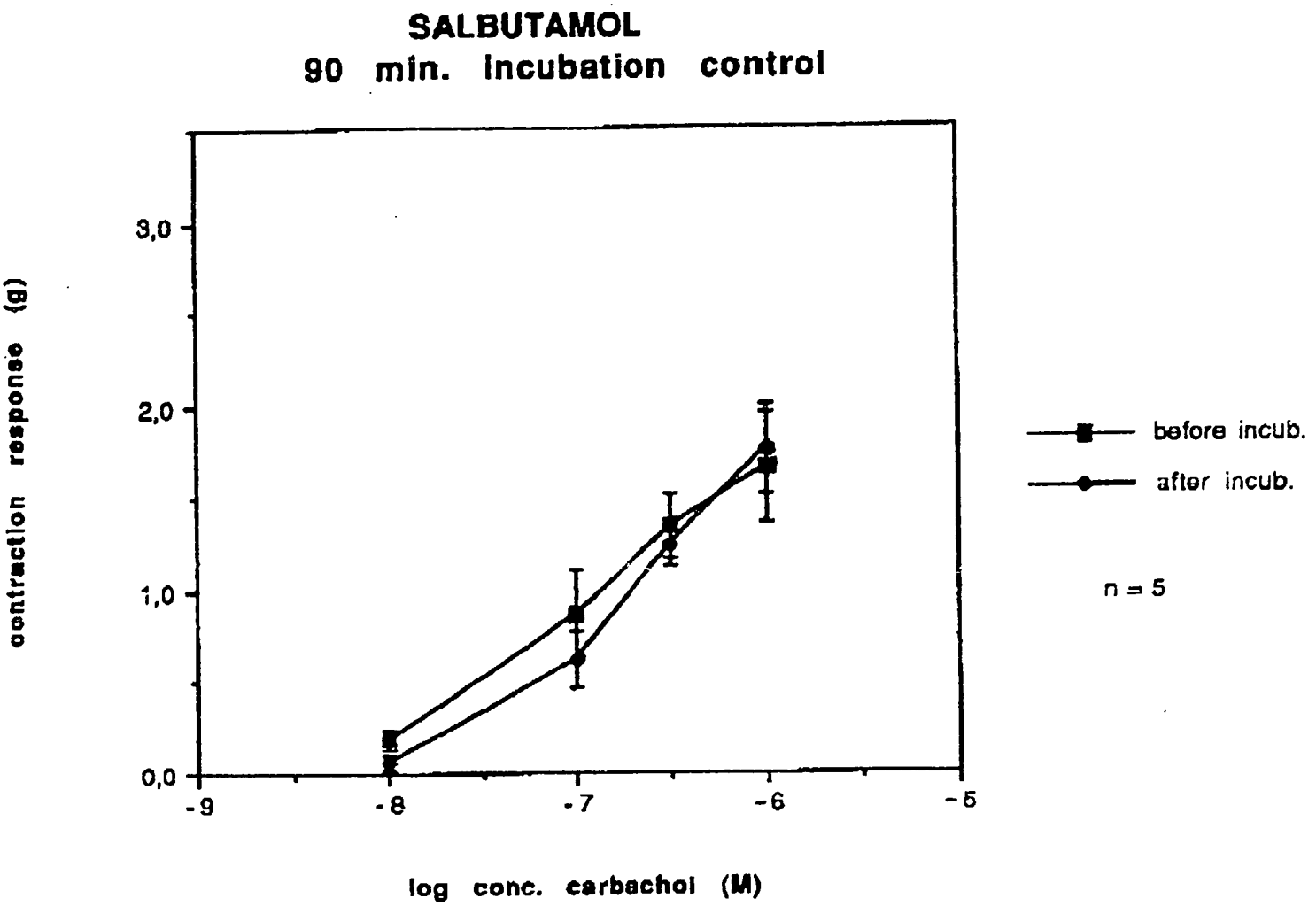

Fig. 1. Dose/response curves for carbacholine concentrations in isolated bronchial smooth muscle preparations. Control experiments.

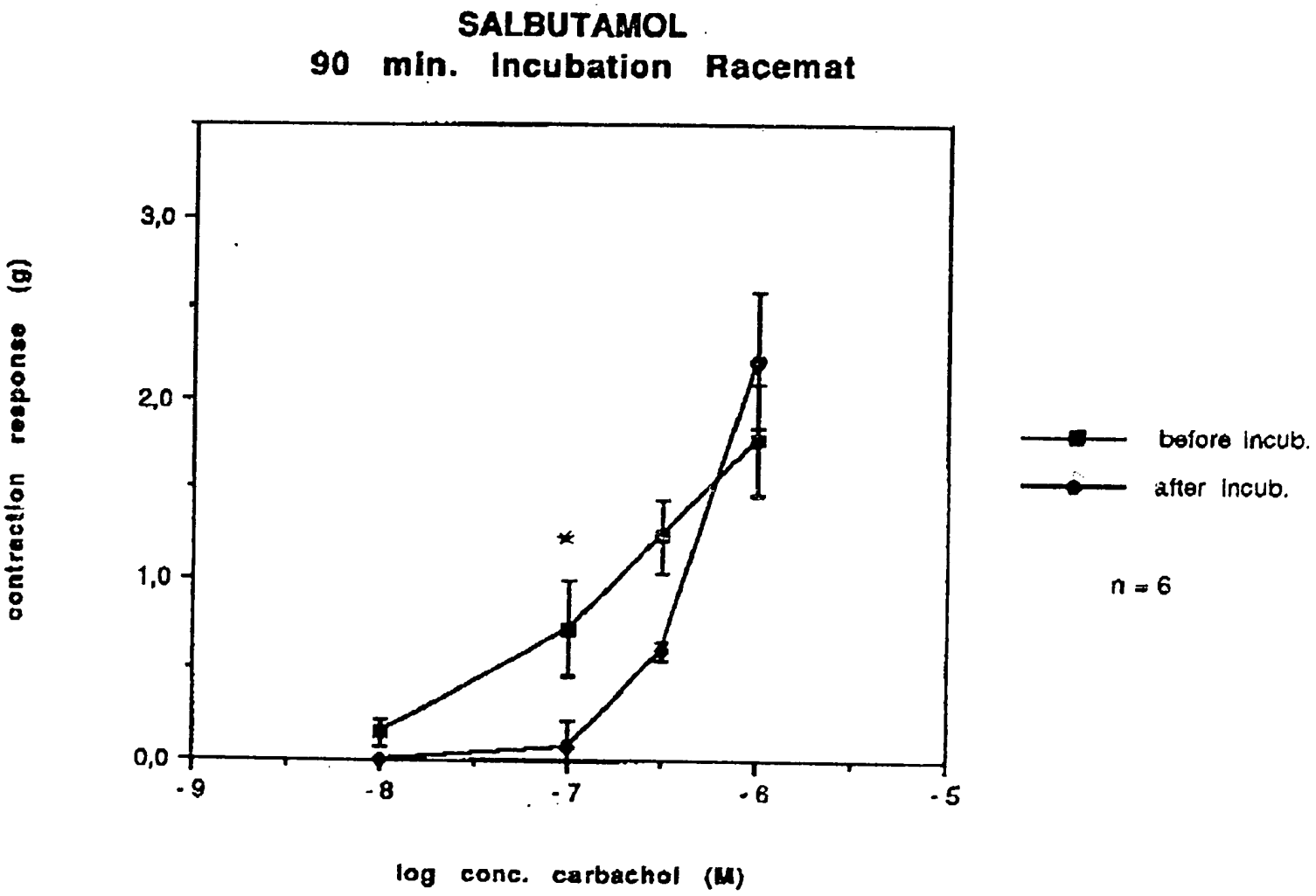

Fig. 2. Dose/response curves for carbacholine concentrations in isolated bronchial smooth muscle preparations before and after incubation with racemic albuterol (salbutamol).

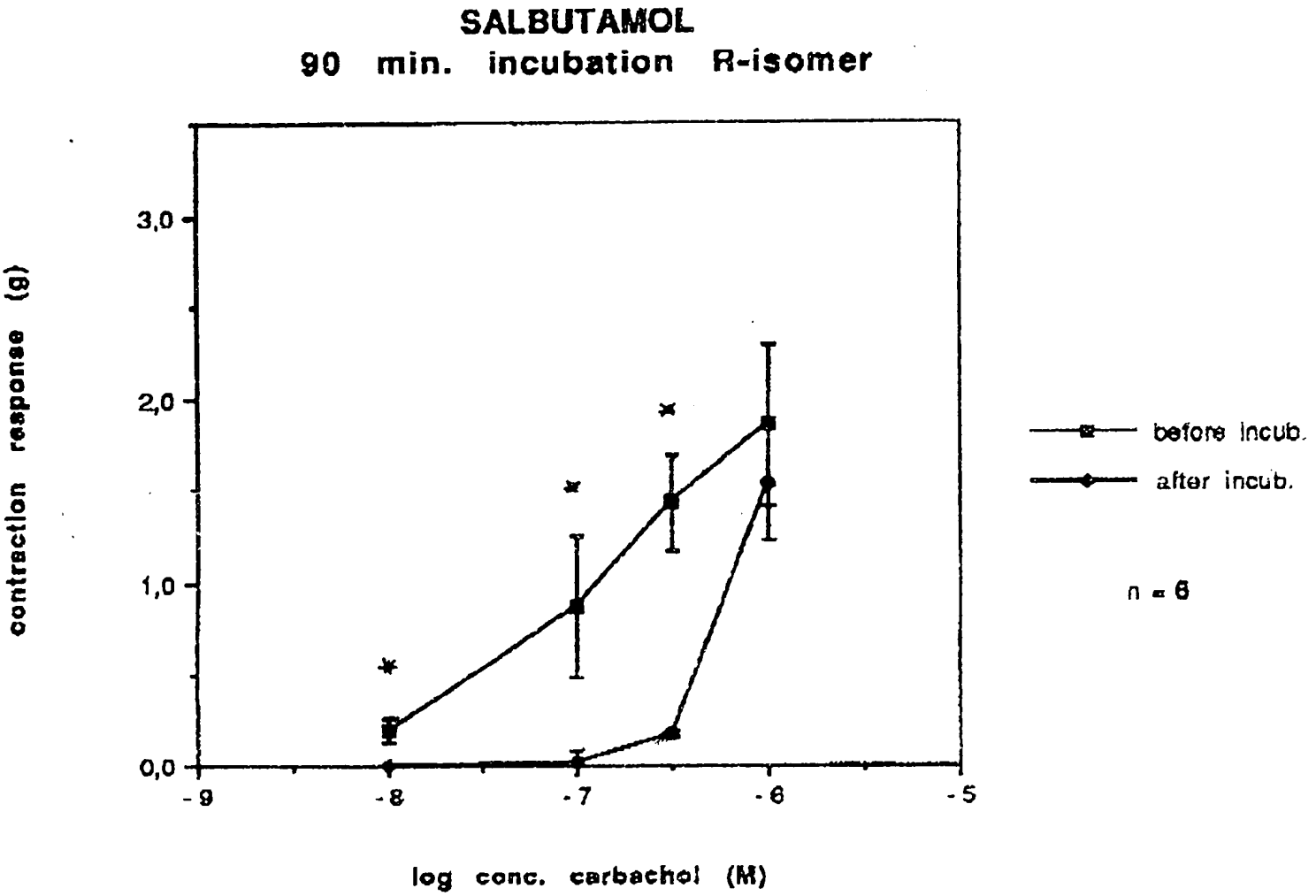

Fig. 3. Dose/response curves for carbacholine concentrations in isolated bronchial smooth muscle preparations before and after incubation with R(-)albuterol (salbutamol).

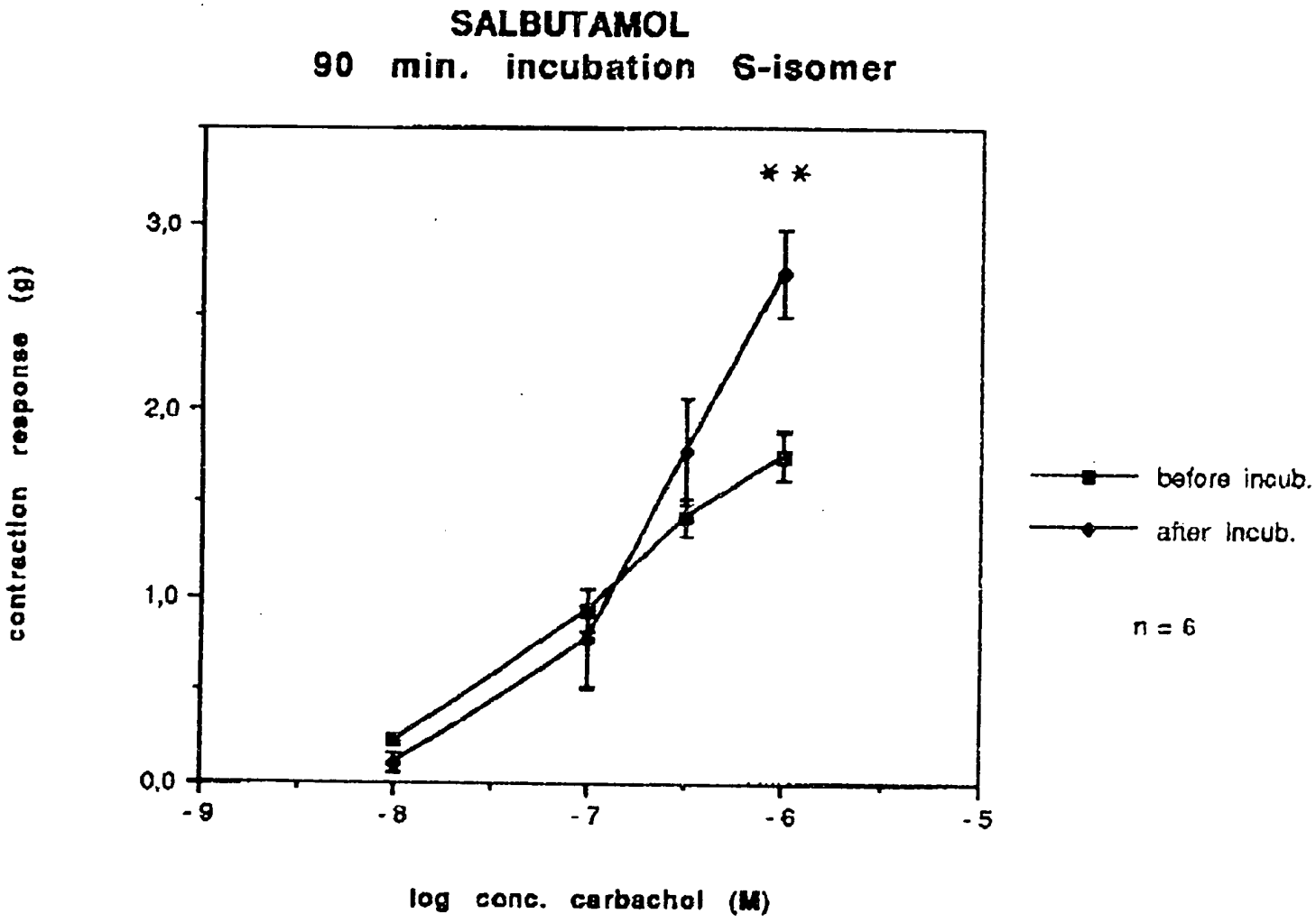

Fig. 4. Dose/response curves for carbacholine concentrations in isolated bronchial smooth muscle preparations before and after incubation with S(+)albuterol (salbutamol).

The experiments of Chapman et al. and Morley et al. in guinea pigs, in conjunction with our above-described studies, are tests which would be accepted by persons of skill in the brochodilator art as predictive of efficacy and of side effects in humans. They would indicate to the person of skill that R(-)albuterol will have a higher therapeutic index than racemic albuterol with respect to the side effect of hypersensitivity.

I further declare that all statements of the foregoing declaration made of my own knowledge are true and that those made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Signed by me this 19th day of July 1993.

Gunnar Aberg